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This document was submitted to EPA by a registrant in connection with EPA's evaluation of this chemical, and it is presented here exactly as submitted.

REGISTRANT RESPONSE TO THE USEPA HAZARD IDENTIFICATION REPORT FOR OXYDEMETON-METHYL

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I. INTRODUCTION

Oxydemeton-methyl (ODM), also known as Metasystox-R™, is an organophosphorous (OP) insecticide registered in the United States and internationally. The US Environmental Protection Agency (EPA) recently issued a Hazard Identification Report for ODM (issued July 24, 1997 from George Ghali, Executive Secretary, Hazard ID Assessment Committee, Health Effects Division). In setting the Reference Dose (RfD) for ODM, the EPA review committee used: 1) a no-observed-effect-level (NOEL) of 0.05 mg/kg/day based on inhibition of plasma (18%) and erythrocyte (14%) cholinesterase in human volunteers receiving 0.1 mg/kg/day; and 2) an uncertainty factor (UF) of 100. The components of the overall UF were based on application of the standard UF of 10 to account for intraspecies variability and an extra UF of 10 based on the reviewers concerns related to mutagenic and delayed neurotoxic potential, steep dose response, use of single sex human volunteers (males only), and some animal brain cholinesterase inhibition at dose levels below those causing inhibition of plasma or red blood cell ChE.

Risk assessments were also done for 1) Acute Dietary Exposure (one-day), UF 100; 2) Short-Term Occupational or Residential Exposure (1-7 days), UF 300; 3) Intermediate Term Occupational or Residential Exposure (>30 days), UF 100 plus an absorption factor of 50%; 4) Chronic Occupational or Residential Exposure, UF 100; and 5) Inhalation Exposure, UF 1000. The uncertainty factors assigned to the various assessments ranged from 100 to 1000. In every case, the EPA included a extra 10X UF for the items discussed above. The Gowan Company believes that the extra uncertainty factors beyond the conservative factors of 10 for intra-species variability and 10 for inter-species variability are not warranted. The Gowan Company also believes that in some cases, the NOEL was misidentified. Therefore, the Gowan Company requests that the uncertainty factors, the RfD, and the various risk assessments be re-evaluated.

II. BACKGROUND INFORMATION

Organophosphate insecticides are thought to exert their toxic effect through the inhibition of the cholinesterase (ChE) enzymes, particularly acetylcholinesterase (AChE) in the central and peripheral nervous system (O'Brien 1967; Carlton 1969; Eaton and Klaassen 1996; Murphy 1986; Zinkl et al. 1979).

The purpose of the ChEs in the tissues is to rapidly hydrolyze the neurotransmitter acetylcholine (ACh) into the inactive fragments of choline and acetic acid after the completion of the neurochemical transmission (Tafuri and Roberts 1987). Acetylcholine is necessary for proper nerve transmission and mediates the transmission of the nerve impulse across the synapse. Inhibition of AChE leads to the accumulation of ACh at synapses which results in continual stimulation of nerve fibers and eventual failure of nerve or muscle repolarization and function

(O'Brien 1967). The resulting disruption of neural transmission occurs in both the central and the peripheral nervous systems (Tafuri and Roberts 1987). Butyrylcholinesterase which is found primarily in the plasma has no known definitive function.

In the case of organophosphate (OP) pesticides, EPA regulates the compounds based on inhibition of cholinesterase (ChE), which is a measure of a molecular event and is not a direct indication of toxicity. In regulating a compound, EPA calculates a reference dose based on experimental data and the use of uncertainty factors. According to EPA (Sette, 1997), "A reference dose (RfD) is an estimate, with uncertainty spanning perhaps an order of magnitude, of a daily exposure to human populations, including sensitive subgroups, that is likely to be without appreciable risk of deleterious effects during a lifetime, i.e., RfD = NOEL/UF". Application of uncertainty factors typically involves use of 10 for intraspecies differences and 10 for interspecies extrapolation, a total of 100, as standard factors for systemic toxicity. Comparable evaluations for acute, short term, or intermediate exposures are derived in exactly the same way." Simplistically, the RfD is derived from the experimental results from toxicologic evaluations of a chemical compound and utilizes the most sensitive indicator of toxicity from these evaluations as the toxicologic endpoint. The No Observed Effect Level (NOEL) from the critical study is used to calculate the RfD by application of uncertainty factors. Typically, a 10X UF is used for intraspecies differences and 10X UF is used for interspecies differences. Thus, a single 10X is used for NOELs derived from human data and an additional 10X (total of 100X) is used for animal studies.

When data are available from human studies with cholinesterase-inhibiting compounds, the Agency uses decreased blood ChE activity as the critical effect. However, inhibition of ChE is not necessarily an indication of toxicity.

Plasma ChE activity is influenced by a variety of factors such as stress, physical condition, diurnal cycles, reproductive cycles, and medication (Bignami et al. 1975; Hill and Murray 1987; Hill 1989; Fairbrother et al. 1989). Northern bobwhite quail (*Colinus virginianus*) removed from a group cage and placed in individual cages showed significantly reduced ChE activity from pre-move levels or from subsequent weekly sampling after adaptation to the new cages (Carlock 1992). Hill and Murray (1987) monitored various species of captive birds over a period of a year and found that plasma ChE activity levels were significantly different at different seasons while brain ChE activity remained stable throughout the various seasons. The work of these researchers and others demonstrates that reduction in plasma ChE activity by itself is not indicative of OP exposure.

The UK Pesticide Safety Directorate (UK PSD) considers plasma ChE to be of no toxicological significance for determination of No-Observed-Effect-Levels, and does not rely on it for risk assessment purposes, unless no other form of ChE is measured. However, it should be restated that the natural variability in plasma ChE activity is considerably larger than that of RBC ChE both within and between species. Plasma ChE has no direct relationship to neuronal AchE, and is composed of two separate liver produced enzymes which vary in proportion depending on the species. These differences indicate that plasma ChE is an inappropriate model for neuronal ChE activity and is an inappropriate biomarker for assessing cholinergic effects.

Large inter-individual and intra-individual variations in normal human RBC ChE activity have been recorded in clinical (Maynard and Breswick, 1992) as well as occupational situations. Fluctuations as great as 13-25% for RBC ChE activity in the same unexposed individual have been reported (Hayes, 1982). Due to the natural variation in ChE activity, it is difficult to determine the degree of change that may be interpreted with confidence as inhibition rather than random variation (Hayes, 1982; Lotti, 1995). The Joint FAO/WHO Meeting on Pesticide Residues (JMPR) recommended that a reduction of greater than 20% of the RBC AChE be used as a regulatory endpoint. This is the value that is most often used by international regulatory agencies. However, the Deutsche Forschungsgemeinschaft (DFG, 1995) and the American Conferences of Government Industrial Hygienists (US ACGIH, 1993) recommend a threshold of greater than 30% decrease in RBC ChE activity for human exposure concerns.

The Acute Cholinesterase Risk Assessment Work Group (ACRA, 1997), presented an extensive peer reviewed paper to EPA's Scientific Advisory Panel (June 3-4, 1997 meeting) that proposed a systematic evaluation of all existing data for cholinesterase-inhibiting compounds in a step wise fashion. The criteria developed were based on actual data from over 80 mammalian toxicology studies with cholinesterase inhibiting compounds. The criteria presented by ACRA is consistent with criteria used by other regulatory agencies, such as California Department of Pesticide Regulation (CADPR), World Health Organization (WHO), United Kingdom Pesticide Safety Directorate, and Health Canada Pesticide Management Regulatory Agency. Based on experimental evidence, sound science and current knowledge, ACRA proposed using the following criteria in conducting risk assessments for acute or short-term exposures to cholinesterase inhibiting compounds.

1. Plasma ChE inhibition is not an adverse effect, and therefore should not be utilized in risk assessments.
2. Red blood cell AChE is not associated with the nervous system, and inhibition is not per se an adverse (neurotoxic) effect.
3. When available, cholinergic effects and/or brain AChE inhibition data should take precedence over RBC AChE for determining No-Observed-Effect-Levels (NOELs);
4. When available, human RBC AChE inhibition or cholinergic effects data should always take precedence over animal data for determining NOELs.
5. Due to the lack of adversity associated with inhibition of RBC AChE, the use of a tenfold (10x) uncertainty factor from the NOEL is adequate when RBC AChE inhibition data from either animal or human studies is used to assess human risk.
6. Due to greater potential for adversity, NOELs for brain AChE inhibition and cholinergic effects identified in animal studies should receive a default uncertainty factor of 100x; lower uncertainty factors may be used on a case-by-case basis.

7. NOELs based on cholinergic effects noted in human studies should only require a 10x uncertainty factor, since an interspecies extrapolation factor from animals to humans is unnecessary.
8. For RBC and brain AChE activity, the threshold for defining a NOEL should be less than or equal to 20% difference from control activity in all species. Based on the biology and the methodologies used, statistical significance can be utilized as a criterion for increasing (but not decreasing) the 20% difference threshold.
9. For risk assessment purposes, duration and route of administration used in the study should reflect the expected duration and route of exposure for humans (i.e. a 21-Day or 28-Day dermal study for subchronic occupational dermal exposure assessment).
10. When dermal data are not available, a subchronic oral toxicity study and an appropriate dermal penetration factor should be used. A general default of 10% absorption should be used, analogous to the UK and German exposure models which are widely used in Europe.

III. REFERENCE DOSE

The critical study used for establishment of the reference dose (RfD) evaluated the effects of ODM on human plasma and RBC ChE activity (Doull et al. prior to 1972; MRID 00039839). ODM was administered either as a solution dissolved in corn oil or non-diluted in gelatin capsules to male volunteers at dosage levels of 0.0125 to 1.5 mg/kg/day for up to 120 days. Dosage levels were calculated from body weight of each volunteer at the time of exposure. Just prior to dosing, blood was drawn for pre-exposure analyses. Each individual was hospitalized and under constant medical supervision during pre-exposure, exposure and post-exposure phases of the study. Individuals received either a single dose or repeated daily doses of ODM. In addition to urinalysis, hematologic and cholinesterase evaluations, the volunteers were monitored for any signs or reported symptoms of toxicity. None of the individuals from any of the dosage levels tested reported/exhibited cholinergic symptoms or other signs of toxicity during the exposure or post-exposure periods. There were no significant changes in any of the hematologic parameters or urine evaluations. The only parameter affected by ODM was decreased ChE activity (plasma and RBC) at doses of 1.0 mg/kg and above for acute exposure and 0.1 mg/kg/day and above for repeated exposures. One individual received 0.4 mg/kg/day for five days, at which time the plasma ChE was decreased more than 50% and the RBC ChE activity was decreased by about 35% when compared to pre-dosing values. At 0.1 mg/kg/day, plasma ChE reached a maximum 40% decrease in activity when compared to pre-exposure activity after two weeks of treatment, while RBC ChE reached a maximum decrease of 50% by day 60 of a 120 day exposure period. There were no decreases in plasma or RBC ChE activity in subjects receiving 0.05 mg/kg/day for up to 60 days.

Based on the results of this human oral toxicity study, the NOEL for acute exposure cholinesterase inhibition (plasma and RBC) is 0.5 mg/kg. The NOEL for for repeated exposure ChE effects was 0.05 mg/kg/day. The NOEL for cholinergic effects was 0.4 mg/kg/day for repeated exposure and 1.5 mg/kg for a single exposure. Since this was a human study where the critical regulatory effect is a measure of a well defined molecular event, the 10-fold uncertainty factor for intraspecies variability takes into account sex, age, and health differences. Thus, there is no need for any additional uncertainty factors to account for use of a single sex. EPA also cited a steep dose response as part of the justification for adding an additional UF to the RfD calculation. In this study, there was very little difference in the degree of ChE inhibition seen at 0.4 mg/kg/day (35% for RBC at day 5) versus 0.1 mg/kg/day ((50% for RBC by day 60). In both cases there was no indication of toxicity from ingestion of Metasystox, only an indication of exposure to the compound.

IV. NEED FOR ADDITIONAL UNCERTAINTY/SAFETY FACTORS?

A. Genotoxicity Concerns

ODM has been classified as genotoxic based results from assays with bacterial and cultured mammalian cells, and from a variety of in vitro studies. However, ODM is not carcinogenic to rats or mice nor did it produce in vivo clastogenic effects in the bone marrow cells of treated Chinese hamsters. Reproduction studies found no inheritable or genetic defects from chronic ingestion of ODM. Similarly, there was no evidence of any developmental effect from in utero exposure to ODM. Therefore, the use of an additional uncertainty factor for possible genetic effects is unwarranted.

B. Plasma, RBC and Brain ChE Inhibition

With regard to animal data, the EPA review committee expressed a concern that some animal data indicated that brain ChE was inhibited at dose levels below those causing plasma and RBC ChE inhibition. A series of 14-day studies were conducted with rats to evaluate ChE effects of ODM (94.6% a.i.) after varying routes of administration (oral gavage, dermal application, and dietary; MRIDs 40499303, 40499304 and 40499302, respectively). While at first glance it appears that brain ChE was inhibited at dose levels below those causing plasma or RBC ChE inhibition, a careful evaluation of the data shows that this anomaly is likely an artifact of evaluating small numbers of animals at each dose level, inherent variability in ChE activity levels, and the analytic methods used, resulting in very low standard deviations. Also since plasma ChE is produced in and secreted by the liver, an initial depression in plasma ChE activity after exposure to low levels of OPs is often followed by a rebound effect, where the liver secretes greater levels of ChE resulting in a net increase in plasma ChE activity. This phenomena was observed in females in the 14-day oral gavage and dermal studies. In the oral gavage study females receiving 0.15 mg/kg had 127% of control plasma ChE activity on Day 7 and 107% on Day 14. In the dermal absorption study, females receiving 0.3 mg/kg had 105% of control plasma ChE activity on Day 7 and 101% on Day 14.

Brain cholinesterase results from the combined chronic toxicity/carcinogenicity study in rats suggested dose-related inhibition at the lowest dose level of 0.027 mg/kg/day (MRID 00151806,40865201, 40865202, 40865203, 44141301). Study results showed brain cholinesterase was inhibited by 11% for males and 6 % for females at 1-month and 8% for males and 9% for females at 27-months (not 89% and 88% inhibition as reported in the ODM Hazard Identification Document). To resolve Agency concerns regarding a lack of a NOEL for brain cholinesterase in this chronic study, additional brain cholinesterase measurements were conducted in a recently conducted 90-day rat feeding study (MRID 44141301). In this study, the NOEL for plasma, RBC and brain ChE effects was 1 ppm. In this study, all three types of ChE (plasma, RBC and brain) showed significant decreases at 10 ppm with the exception of plasma ChE activity in females at Week 4. In this case the plasma ChE activity of females receiving 10 ppm decreased by 30% when compared to controls, but due to the large variability (and standard deviations) this value was not statistically significant. The results of this study do not support the hypothesis that plasma and RBC ChE are less sensitive than brain ChE to inhibition by ODM.

Clemens et al. (1990) assessed the embryotoxic, fetotoxic, and teratogenic potential of ODM through an extensive series of evaluations on 180 mated female rats. This study also evaluated the effects of maternally toxic doses of ODM on fetal brain AChE, neonatal survival, growth, physical or neurobehavioral development. Pregnant rats received daily ODM doses at 0, 0.5, 1.5 or 4.5 mg/kg from Day 6 to 15 of gestation. On Day 16, plasma ChE in the dams was inhibited 30.0%, 54.2% and 71.6% in the 0.5, 1.5 and 4.5 mg/kg groups, respectively, while brain ChE was inhibited 21.5%, 51.9% and 68.2%. The degree of RBC ChE inhibition was slightly less, 18.4%, 37.3% and 55.7%, but the pattern of depression was similar. Rats receiving 4.5 mg/kg also showed reduced food consumption, suppressed body weight gain, and tremors. There was no evidence of embryotoxic, fetotoxic or teratogenic effects at any dose level, even at a level producing overt maternal toxicity. Fetal brain ChE was not inhibited at any treatment level, even though the dams themselves exhibited significant inhibition of brain, plasma and RBC ChE activity. Furthermore, neonatal survival, growth and development were unaffected and extensive neurobehavioral evaluations demonstrated no alteration of sensory or reflex functions, maze learning ability, or open field activity for neonates. Clearly, no differences in sensitivity of the various ChE to ODM was demonstrated in this study.

Based on the results of multiple studies, it is apparent that plasma, RBC and brain ChE are all similarly affected by exposure to ODM. Thus, there is no need to include an extra uncertainty factor to account for apparent differential sensitivity resulting from varying degrees of analytical precision for different ChE containing tissues (plasma, RBC and brain), natural variations in ChE activity of different tissues, sample size, and statistical significance.

C. Delayed Neurotoxicity

With regard to evidence of delayed neurotoxic potential, this judgement was based on a 1984 acute delayed neurotoxicity study where ODM (50% concentrate) was administered at the approximate median lethal dose (200 mg/kg) to chickens, which were then treated aggressively with the antidotes atropine and 2-PAM (MRIDs 00145105 and 40860001). However, when chickens received technical grade ODM (92.6% purity) at dose levels of 0, 1, 5 or 10 mg/kg/day for 13 weeks (5 days/week), there were no indications of neurotoxicity or any increase in microscopic neurological lesions.

In mammalian studies there was no evidence of delayed neurotoxicity after exposure to ODM. In an acute neurotoxicity study (MRID 43929901), rats were dosed with 0, 2.5, 10 or 50 mg a.i./kg of a 50% formulation of ODM. At 10 mg/kg, a variety of cholinergic signs were observed (tremors, ataxic gait, pin-point pupils, and decreases in body temperature, defecation, arousal, pinch response, etc.. At 50 mg/kg, weight loss occurred and motor and sensory impairment were noted. Approximately 15 Functional Operational Battery (FOB) parameters were affected and some animals died. The FOB changes were generally limited to the time-of-peak-effect FOB and motor activity observation interval (1.5 to 2.25 hours post dosing). The ODM treated animals were asymptomatic at the Day 7 and Day 14 FOB and motor activity intervals. No histopathologic changes of neural tissues were noted for the ODM treated animals. Plasma, RBC and brain ChE were inhibited at all ODM dose levels in a dose dependent manner with similar degrees of inhibition for each tissue. However, even though plasma and brain ChE were decreased 45 and 55% (respectively) on Day 0, neither of these values were statistically significant. Despite the lack of statistical significance, the NOEL for ChE effects was concluded to be < 2.5 mg/kg. The NOEL for cholinergic effects was 2.5 mg/kg. Pathology evaluations found no lesions associated with ODM treatment. Thus, there was no evidence of delayed neurotoxicity in rats exposed to ODM.

In a subchronic neurotoxicity study (MRID 44189501), rats received 0, 1, 10 or 80 ppm ODM for 13 weeks. Plasma, RBC and brain ChE activity levels were significantly decreased at 10 and 80 ppm but not at 1 ppm. No clinical signs were noted at 10 ppm, but at 80 ppm body weight was decreased and some animals exhibited tremors, aggressive behavior and fur staining. No FOB parameters (except hindlimb grip strength which was considered to be related to the weight decrease more so than an actual neurotoxic effect) or motor activity were affected at any dose level. There were no histopathological findings (lesions) related to treatment with ODM and no evidence of delayed neuropathy. The NOEL for ChE effects was 1 ppm (0.062 mg/kg/day for males, 0.074 mg/kg/day for females). The NOEL for cholinergic effects was 10 ppm (0.62 mg/kg/day for males, 0.75 mg/kg/day for females).

Evaluation of human patients after suicide attempts and poisonings with large doses of ODM, provide no evidence of any delayed neurotoxicity (Carrington da Costa et al., 1982; Kleinschmidt et al. 1994). Successful cardio-respiratory resuscitation and aggressive therapy with atropine and obidoxime after a suicide attempt with ODM allowed a 52 year old woman to recover completely after 14 days of treatment (Kleinschmidt et al., 1994). Since there is no evidence of delayed neurotoxicity in mammals or birds from subchronic or chronic exposure to non-lethal doses of ODM and the human suicide/poisoning data indicate no evidence of long term effects or neurotoxicity, the relevance of the putative acute delayed neurotoxicity in chickens as a predictor of human effects is extremely tenuous and does not warrant adding another safety factor to an already conservative uncertainty factor.

Therefore, based on the extent and the adequacy of the available data, there is no justification for adding an additional UF to the RfD calculation. Using the standard method of calculating the RfD (RfD = NOEL/UF), using a NOEL of 0.05 mg/kg/day and a conservative UF of 10 (to account for intra-species variability), the RfD should be 0.005 mg/kg/day.

V. ACUTE DIETARY EXPOSURE (One Day)

The critical study used for the Acute Dietary Exposure Risk Assessment is the same human oral toxicity study that was used to establish the RfD. The Gowan Company agrees with the choice of the critical study for this evaluation, but disagrees with the endpoint selection and the choice of uncertainty factors that the EPA review committee recommends. The study clearly demonstrated that the acute NOEL was 0.5 mg/kg based on plasma cholinesterase inhibition of 18% and erythrocyte cholinesterase inhibition of 14% seen after dosing with 1.0 mg/kg. This was recognized by the Agency in its review (Data Evaluation Record) of the study. The Gowan Company believes that an uncertainty factor of 10 to account for intra-species variability is warranted, but the use of additional uncertainty factors is unwarranted as previously detailed. Therefore, the RfD for Acute Dietary Exposure should be 0.05 mg/kg/day (0.5 mg/kg/day/10 =0.05 mg/kg/day).

VI. SHORT-TERM OCCUPATIONAL OR RESIDENTIAL EXPOSURE (One to Seven Days)

The EPA review committee recommended using the 14-day rat dermal study as the critical study for the short-term occupational or residential exposure risk assessment of ODM. Gowan has some technical concerns related to the conduct of the 14-day dermal study and will conduct a new rat dermal study (January, 1998) to resolve these concerns. The new study will be of 7-days duration, the maximum duration for the Short-Term Occupational or Residential Exposure Assessment. The purpose of this study is to resolve the issue regarding brain cholinesterase as the most sensitive indication of ODM exposure. This issue was previously resolved for oral exposure as discussed above.

Regardless of the results from the new rat dermal study, the Gowan Company believes that it is more appropriate to use human data when it is available rather than extrapolate from other lower species. Since the human NOEL of 0.05 mg/kg/day was generated from an oral study, an appropriate dermal absorption factor based on experimental results must be used in the risk calculations. A rodent dermal absorption study demonstrated approximately 50% dermal absorption. However, Bayer Corporation conducted a dermal absorption study in the rhesus monkey, an animal model more consistent with humans. Gowan contends that the results from this monkey study rather than those from the rodent study should be considered in assessing the dermal absorption of ODM. This monkey study demonstrated a maximum 24-hour dermal absorption of 32.9%. The resulting RfD for short-term occupational or residential exposure is expressed as (NOEL/Absorption Factor)/UF. Therefore, based on the arguments presented previously, the short term RfD [(0.05 mg/kg/0.329)/10] should be 0.015 mg/kg/day.

VII. INTERMEDIATE-TERM OCCUPATIONAL OR RESIDENTIAL EXPOSURE

The EPA review committee recommended using the human oral toxicity study as the critical study to use in the Intermediate-Term Occupational or Residential Exposure risk assessment, an uncertainty factor of 100 and the use of a 50% dermal absorption factor . The Gowan Company agrees with the choice of critical study, but does not agree with using the rodent derived dermal absorption factor nor using an uncertainty factor of 100. Since this risk calculation is based on human data, it is appropriate that a UF of 10 to account for intra-species variability be used. The monkey dermal absorption factor of 32.9% should also be used as described above. Therefore, the RfD for Intermediate-Term Occupational or Residential Exposure should be the same as that obtained for Short-Term Occupational or Residential Exposure, 0.015 mg/kg/day.

VIII. CHRONIC OCCUPATIONAL OR RESIDENTIAL EXPOSURE

The EPA review committee recommended using the human oral toxicity study NOEL of 0.05 mg/kg/day and a UF of 100. There was no mention of using a dermal absorption factor. The Gowan Company believes that the risk assessment for Chronic Occupational or Residential Exposure should be based on the human oral toxicity study and utilize a dermal absorption factor (32.9%) and a 10 fold uncertainty factor as described earlier. This would result in a RfD for Chronic Occupational or Residential Exposure for ODM of 0.015 mg/kg.

IX. CONCLUSION

Based on the extent and the adequacy of ODM human and animal toxicity data, there is no justification for adding an additional uncertainty or safety factor in calculated the RfD or acceptable exposure levels. Since human data is the basis for establishing the RfD and the acceptable exposure levels for ODM, use of the conservative UF of 10 to account for intra-species variability, will provide an estimate of acceptable daily exposure to humans that is protective of sensitive individuals and will present neglible risk of deleterious effects during a lifetime.

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